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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,964	11/28/2000	Tessa Crompton	CIBT-P01-080	7789

28120 7590 01/24/2003

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	19

DATE MAILED: 01/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/724,964	Applicant(s) Crompton
	Examiner Michael Brannock	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 29, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above, claim(s) *3, 19, 20, 22-28, and 30* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-18, 21, and 29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 28, 2000* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 6, 9/13/01, and in Paper 16, 8/7/02, have been entered in full.

2. Claims 1-30 are pending.

3. Applicant's election, with traverse, in Paper 16, of Group I, and in Paper 18, 10/29/02, as the claims relate to the administration of a benzene modified sonic hedgehog polypeptide for the inhibition of an immune response, is acknowledged. The examiner finds that claims 1, 2, 4-18, 21 and 29 read on the elected invention. Claims 3, 19, 20, 22-28 and 30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 16 and in Paper 18. Applicant is reminded that claims 1, 2, 4-18, 21 and 29 are being examined in this Office action only to the extent that the claims read on the elected invention.

The traversal is on the grounds that a search of Groups I-II would not be a serious burden on the examiner because the claims of Group II encompass the subject matter of those of Group I. Particularly, Applicant argues that each group is directed to modulating the hedgehog signaling pathway and thus a search of one search would co-extensive with the other. This argument has been fully considered but not deemed persuasive. Each recited method requires different starting materials and accomplishes entirely different goals. Group I requires a search of immuno-suppressive methods which is divergent and not coextensive with a search of

methods of enhancing an immune response. Additionally, Applicant traverses the restriction requirement between Group III and Groups I and II on the basis that group III can be searched simultaneously with either of Groups I or II. This argument has been fully considered but not deemed persuasive. Group III encompasses an essentially limitless number of compounds defined in the specification as hedgehog or ptc therapeutics, such a limitless number of molecules would not be simultaneously searched with the elected method groups. Applicant further traverses the species election requirement, arguing that because the species are in a Markush-type format, and are sufficiently few in number, that all should be examined together. This argument has been fully considered but not deemed persuasive. As set forth previously, each species appears to be a structurally and functionally distinct molecule, the use of one not being required for the use of any other. As there appears to be an essentially unlimited number of species, encompassed by the claims, the number of species could not be sufficiently few so as to fall with in the meaning of MPEP 803.02. Therefore, the restriction is maintained and made final.

Drawings

4. The drawings are objected to as set forth in the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 4-18, 21 and 29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

The claims require a "hedgehog or ptc therapeutic". The specification defines "hedgehog or ptc therapeutic" as that which mimics or antagonizes the effects of naturally occurring hedgehog proteins on patched signaling (see page 6). The specification further appears to define "ptc therapeutic" as a molecule which "binds to patched and alters its signal transduction activity, or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched (see pages 6 and 41). Thus, "hedgehog or ptc therapeutic" appears to encompass any and all compounds that alter the any activity that could be attributed to hedgehog or patched. However, it is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40), therefore the phrase "hedgehog or ptc therapeutic"

renders the claims indefinite because those skilled in the art would have to identify the activities of patched in order to determine whether a compound alters these activities.

Claim 1 requires a method for modulating the immune function of an animal. The word "modulating" renders the claims indefinite because it is unclear what this term is intended encompass relative to the immune function of an animal, e.g. the term encompasses enhancing the immune function of an animal (e.g. claim 3), yet it is unclear what does and does not constitute and enhancement of the immune system, as this phrase is a subjective and relative phrase and the specification has not set forth what is and what is not an enhancement of the immune function of an animal.

Further the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a "hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

The claims require methods of suppressing the immune function or immune system of an animal, comprising administering a "therapeutic amount" or an "effect amount" of a "ptc therapeutic" or a "therapeutically effective amount" of a "ptc therapeutic", yet the claims fail to require that amount be "effect" or "therapeutically effective" at any particular thing or that the amount be protective of any particular thing. Thus, it is unclear what the amount of the "ptc

therapeutic" is "therapeutic" or otherwise "effective" for. Therefore, the metes and bounds of the claims cannot be determined.

Claim 4, and dependent claims, require an amino acid sequence that is homologous to an amino acid sequence. Homology is a relative term and it is used in the art to provide a comparison between two amino acid sequences; yet the term, alone, does not provide a definition of the degree of similarity within the comparison. In the instant case, it is the degree of similarity between the claimed amino acid sequence and the reference sequences that determines the metes and bounds of the claim. As this degree of similarity is not set forth, either in the claims or in the specification, the metes and bounds of the claims cannot be determined.

Claim 7 requires that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, 4-18, 21 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of suppressing or promoting thymic T-cell maturation comprising administering a polypeptide at least 80% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, wherein said peptide binds a naturally occurring patched protein, does not reasonably provide enablement for the broad scope of suppressing or enhancing the immune function or immune system of an animal, nor for modulating T-cell maturation other than in the thymus (e.g. peripheral T-cell maturation), nor for any form of therapy, and nor for the suppression or promotion of T-cell maturation comprising the administration of a hedgehog or ptc-therapeutic or agonist thereof other than a polypeptide at least 80% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents results obtained wherein sonic hedgehog was shown to suppress the transition of dissociated fetal thymic T-cells from the CD4-CD8- double negative stage to the double positive stage. Conversely, an anti-hedgehog antibody appeared to promote the transition from the double negative to the double positive stage (e.g. Figures 1-4). The specification, however, only speculates that hedgehog proteins could have similar effects on

other aspects of the immune system; and that such effects could be utilized as part of a therapy (e.g. pages 4-5 and 9-12). Further, the specification appears to simply speculate that any or some of the myriad of chemically and functionally disparate compounds that are asserted as being "hedgehog or ptc therapeutics" or agonists thereof could be used to accomplish the recited goals of the claims, yet does not provide sufficient guidance to the skilled artisan to chose among them. Each of the above issues will be discussed in detail below.

Claims 1, 2, 4-18 and 21 encompass methods of modulating any and all aspects of the immune system, yet the specification has provided sufficient guidance only as the claims relate to methods of modulating T-cell maturation in the thymus. The skilled artisan appreciates that the immune system comprises an extraordinarily complex and varied array of subsystems and sub-processes which make up those subsystems, as is well established in the art. The instant specification describes some effects of hedgehog signaling on the process of T-cell maturation in the thymus. Yet the claims encompass any and all processes involving the immune system, e.g. B-cell maturation and activation, peripheral T-cell maturation, T-cell activation, etc. (see page 1, for example). The specification provides no teaching as to what can be expected of hedgehog signaling in any process other than thymic T-cell maturation. The specification teaches that hedgehog proteins are antagonists of immune function, e.g. antagonists of T-cell maturation (pg 5, lines 10-16); however, hedgehog proteins are known in the art to act as both positive and negative regulators in an extraordinary variety of developmental and cell-maintenance capacities involving many disparate cell types. Thus, the skilled artisan could not expect to be able predict

the effects of hedgehog on any other immune system component simply based on Applicant's disclosed observations regarding the effect of sonic hedgehog on the CD4-CD8- double negative/double positive transition in the thymus. This fact is evidenced, for instance, by Lowery et al., J. Immunology 169(4)1869-75, 1999, who report that sonic hedgehog promotes, rather than inhibits, cell cycle progression in activated peripheral CD4+ T-cells (see the Abstract); an effect opposite to that of the instantly reported effect on T-cell maturation in the thymus. The skilled artisan appreciates that the instant specification provides only an invitation to try and find other effects that hedgehog proteins might have on any other aspect of the immune system. Thus, in order to practice the invention commensurate in scope to that which is claimed, the skilled artisan is provided with nothing more that an invitation to begin an extensive research plan wherein various components of the immune system are tested against the presence or absence of hedgehog proteins to try to find some effect, and then to try find a way to use that effect for some purpose. Such a call for random trial and error experimentation is unduly burdensome.

Claim 1, and dependent claims, require the administration of a therapeutic amount of a hedgehog or ptc therapeutic. The specification has merely provided a speculation that because sonic hedgehog inhibits the CD4-CD8- double negative/double positive transition *in vitro*, then sonic hedgehog could be used in some form of immune therapy. The skilled artisan appreciates that simply because a substance in inhibits the CD4-CD8- double negative/double positive transition, it does not follow that the substance would be useful in an immune therapy. Ethanol

is known in the art to inhibit the CD4-CD8- double negative/double positive transition *in vivo*, yet ethanol is not used in immune therapy (see Dubec et al., ALCOHOL 13(6)55-537, 1996. Thus, the instant specification provides merely an invitation to the highly skilled artisan to begin a research plan to try to determine what a "therapeutic amount" of sonic hedgehog is, as it relates to immune function, if, indeed, a "therapeutic amount" of sonic hedgehog can be found.

Additionally, the specification has provide results with the administration of the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide or an anti-hedgehog antibody, such fragment being known to bind patched protein, yet the claims comprise an essentially unlimited genus of proteins that would not be expected to bind mammalian patched, e.g. artificial proteins, and proteins being 80% identical to the full length sonic hedgehog could be substantially less identical to the N-terminal fragment, etc. The claims are not limited to the use of the proteins that could be reasonably expected to bind a naturally occurring patched protein.

Further, the claims encompass the administration of any compound that is encompassed by the definition of a hedgehog or ptc-therapeutic, i.e., any compound that "binds to patched and alters its signal transduction activity, or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched"(see pages 6 and 41). It is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely

identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40). The claims claim methods of modulating or suppressing the immune system with hedgehog or ptc therapeutics, yet the specification does not provide sufficient guidance as to which hedgehog or ptc therapeutics are useful modulating any particular aspect of the immune response. The specification puts forth that PKA inhibitors are ptc-therapeutics and that high PKA activity has been shown to antagonize hedgehog signaling (page 48); yet the specification merely invites the artisan to test these PKA inhibitors to try to find ways in which they might effect the immune system. The involvement of PKA, and cAMP in general, in T-lymphocyte maturation and/or activation has been studied *in vitro* for years; such study has revealed a complex and unpredictable relationship between PKA and the activity of T-cells, reviewed in Bryce et al., Immunopharmacology 41(139-146)1999. In fact, Bryce et al. teach that the immunomodulatory effects of cAMP on T-cells do not involve PKA (see the Title) and suggest that the previously reported effects of PKA inhibitors on T-cells (e.g. that of claim 23) are due to nonspecific interactions with other kinases (see col 1 of page 140). The instant specification, has not provided the skilled artisan with more than an invitation to try to find compounds that are encompassed by the term "hedgehog or ptc-therapeutic" and then to try to find effects of the compounds on any aspect of the immune system. Such essentially random trial and error experimentation is not considered routine by the skilled artisan and would be considered unduly burdensome.

Therefore, due to the lack of direction/guidance presented in the specification regarding which structural features are required of a ptc-therapeutic in order to provide activity, the absence of working examples directed to same, the complex nature of the effect of compounds disclosed as being hedgehog or ptc therapeutics and the contradictory state of the art (see Stull and Iacovitti, Dubec et al., Lowery et al., and Bryce et al., above), the breadth of the claims which encompass a multitude of distinct and disparate aspects of the immune system, and which encompass a multitude of functionally disparate ptc-therapeutics, undue experimentation would be required of the skilled artisan to make the claimed invention.

9. Claims 1, 4-18, 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require *in vivo* methods of modulating an immune response comprising administering a "therapeutic amount" of "hedgehog or ptc therapeutic". However, there appears to be no description of such a therapeutic amount in the specification. The specification appears to base the assertion of potential therapy on the observed effects of sonic hedgehog on T-cell maturation in an *in vitro* thymic cell preparation, e.g. that sonic hedgehog inhibits the CD4-CD8- double negative/double positive transition *in vitro*. The skilled artisan recognizes, however, that simply because a substance in inhibits the CD4-CD8- double negative/double positive transition,

it does not follow that the substance would be useful in an immune therapy. Ethanol is known in the art to inhibit the CD4-CD8- double negative/double positive transition *in vivo*, yet ethanol is not used in immune therapy (see Dubec et al., ALCOHOL 13(6)55-537, 1996. Thus, based on Applicant's limited disclosure, the skilled artisan would not recognize that Applicant was in possession of a therapeutic amount of sonic hedgehog for the modulation of the immune system, as is required by the claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

January 22, 2003

Yvonne Eyler

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